existing mural thrombus in a well characterized porcine perfusion system in which a fresh mural thrombus was formed by perfusing severely injured arterial wall with porcine blood for 5 min at a shear rate of 1690/s (corresponding to a moderate coronary stenosis). Thrombus formation was measured by morphometric analysis. The average mural thrombus achieved in 5 min was 0.135 mm^2/mm (n = 17).

To quantify the growth of thrombus, MT was perfused with whole blood of control and treated animals at the same flow conditions.

Thrombus growth on MT was evaluated in pigs treated with Placebo, Aspirin (ASA, 5 mg/kg iv), Heparin (Hep, 100 IU/kg/h) plus ASA iv, high-dose Hep (250 IU/kg/h iv), and r-Hirudin (1 mg/kg/h iv) as a probe for thrombin. Anticoagulation was evaluated by aPTT (sec). Results expressed as thrombus area (TA mm^2/mm, ± SEM) and % growth of thrombus (GT) on MT were compared by Anova:

	Placebo	ASA	Hep + ASA	Hep 250	r-Hir
n	28	13	6	14	13
TA	0.29 ± 0.01	0.28 ± 0.02	0.20 ± 0.02*	0.15 ± 0.01*	0.07 ± 0.01*#†
%GT	+119 ± 14	+110 ± 11	+48 ± 12*	+13 ± 5*	−48 ± 2*#†
aPTT	31 ± 3	32 ± 5	46 ± 2	>300	68 ± 3

$p < 0.05$; * vs Placebo; # vs hep250, † vs MT

These data suggest that by directly inhibiting thrombin activity, r-hirudin completely inhibits growth of thrombus and is more effective al lower levels of anticoagulation than the highest does of heparin. Specific thrombin inhibition also leads to an overall reduction of the mural thrombus at shear rates typical of a moderate coronary stenosis indicating deaggregation of a pre-existing mural thrombus.

3:00

797-5 Ulceration of Smooth Muscle Cell-Rich Plaques: A Frequent Cause of Coronary Artery Thrombosis That is not Mediated by HLA-DR Expression

Andrew Farb, Anita L. Tang, Allen P. Burke, Youhai Liang, Poonam Mannan, John Smialek, Renu Virmani *Armed Forces Institute of Pathology, Washington, DC*

Coronary artery thrombosis (CAT) is reported to occur primarily from plaque rupture (PR) involving disruption of a fibrous cap over a necrotic core. However, CAT associated with superficial ulceration (SU) of predominately fibromuscular plaques without rupture of a necrotic core is under-reported. We performed post-mortem angiography, detailed coronary histology, morphometry, and immunohistochemistry in 42 cases (33 men, 9 women) of sudden death due to CAT. All individuals died ≤6 hours of symptom onset. Histo- and immunochemical stains consisted of Movat pentachrome, H&E, smooth muscle specific actin, KP-1 (for macrophages), UCHL1 (for T-cells), Leder stain (for neutrophils), and HLA-DR. *Results:*

	Age (yr)	SMCs	MACs	T-cells	PMNs	NC	CAL
PR, n = 24	52 ± 10	8%	67%	100%	8%	83%	71%
SU, n = 18	44 ± 7	61%	22%	36%	28%	33%	28%
p-value	<0.02	<0.001	<0.01	<0.005	0.12	<0.01	<0.02

SMCs (= smooth muscle cells), MACs (= macrophages), T-cells, and PMNs (= neutrophils) in plaque adjacent to thrombus; NC = large necrotic core; CAL = calcified plaque

The luminal surface of SU plaques contained accumulations of SMCs within a proteoglycan matrix. In PR cases, the ruptured fibrous cap was typically infiltrated by MACs and T-cells. Expression of HLA-DR antigens was present in MACs and T-cells in 62% of PR cases and expressed in SMCs in 14% of SU cases ($p < 0.02$). The percent luminal area stenosis was 79 ± 13% in PR and 71 ± 14% in SU, $p < 0.05$. No differences in plaque eccentricity or occlusive vs. non-occlusive thrombi were noted. *Conclusions:* Superficial ulceration of smooth muscle cell-rich plaques lacking plaque rupture into a large necrotic core is a frequent (43%) finding in coronary thrombosis and is more often seen in younger persons with non-calcified plaques and less luminal narrowing. The mechanism of coronary artery thrombosis in plaques rich in SMCs is not mediated by HLA-DR expression and warrants further study.

3:15

797-6 Recombinant Lys-Plasminogen Given Prior to, but not After, Tissue-Plasminogen Activator Markedly Improves Coronary Thrombolysis in Dogs

Liying Chen, Wilmer W. Nichols, Tom G.P. Saldeen, Jawahar L. Mehta. *University of Florida, Gainesville, FL; VAMC, Gainesville, FL*

Tissue-plasminogen activator (t-PA) activates plasminogen to plasmin which results in clot lysis. While t-PA administration rapidly restores blood flow in the thrombosed coronary artery, the coronary artery often reoccludes after initial thrombolysis. We hypothesized that administration of lys-plasminogen, which binds to fibrinogen with 10 times greater affinity and results in a loose fibrin structure (vs native glu-plasminogen) may enhance the thrombolytic efficacy of t-PA. To examine this hypothesis, dogs with electrically-induced stable thrombus in the LAD coronary artery were treated with saline (n = 10) or lys-plasminogen (2 mg/kg, n = 5) followed 10 minutes later by t-PA (1 mg/kg over 20 min). Five other dogs with occlusive LAD thrombus were first given t-PA followed by lys-plasminogen (2 mg/kg) 40 minutes later. Blood flow characteristics were observed for 2 hours. Lys-plasminogen given before t-PA restored flow in all dogs (vs 75% in saline + t-PA group) in 14 ± 4 minutes (vs 24 ± 3 minutes, $P < 0.05$) lasting <2 hours (vs 41 ± 5 minutes, $P < 0.02$) with coronary reocclusion rate of 0% (vs 71%, $P < 0.02$). In dogs given lys-plasminogen after t-PA, the reperfusion rate was 75%, time to reflow 32 ± 6 min, duration of flow 25 ± 19 min and the reocclusion rate 75% ($P < 0.05$ vs dogs given lys-plasminogen before t-PA; P-NS vs dogs given saline + t-PA). Thus recombinant lys-plasminogen given *before* t-PA markedly decreases time to thrombolysis and results in sustained thrombolysis. In contrast, lys-plasminogen given after t-PA has no effect on these parameters of thrombolysis. Enhanced binding of lys-plasminogen to fibrinogen in the thrombus resulting in easily dissolvable clot structure may be the basis of these observations.

798 Antiarrhythmic Drug Therapy

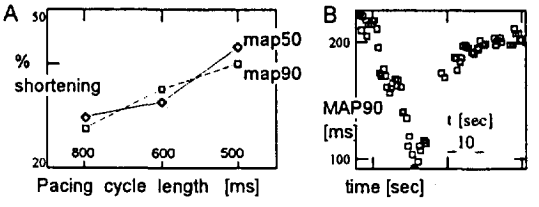
Wednesday, March 22, 1995, 2:00 p.m.–3:30 p.m.
Ernest N. Morial Convention Center, Room 103

2:00

798-1 Electrophysiological Effects of Adenosine on Human Monophasic Action Potentials

Damijan Vokac, Mario Talajic, Tomy Hadjis, Marc Dubuc, Denis Roy, Stanley Nattel. *Montreal Heart Institute, Montreal, Quebec, Canada*

Administration of adenosine (Ad) frequently terminates reentrant supraventricular tachycardias and may precipitate atrial fibrillation. We characterized the electrophysiologic effects of incremental doses (1, 3, 6 mg) of Ad in 8 pts (age 24–60) during elective electrophysiologic study. Ad was administered via a central catheter during pacing at cycle lengths (CL) of 800, 600 and 500 msec. Monophasic action potentials (MAP) were simultaneously recorded from the RA and RV and analyzed off-line. *Results:* Ad decreased atrial MAP at 90% repolarization (CL 600 msec) by 14, 28 and 35% (1, 3, 6 mg respectively). Ad's atrial effects were rate-dependent (graph A) and dissipated with a mean time constant of 3.2 ± 0.58 msec (graph B).



In conclusion, Ad causes marked shortening of human atrial action potential at doses even lower than those used clinically. These effects are rate-dependent and may account for induction of atrial fibrillation by Ad.

2:15

798-2 Differential Sensitivity of AV and VA Conduction to Adenosine in Humans

Wen-Ter Lai, Sheng-Nan Wu, Chee-Siong Lee, Jung-Chou Wu, Sheng-Shiung Sheu, Yeo-Shin Hwang, Luiz Belardinelli. *Kaohsiung Medical College, Kaohsiung, Taiwan; University of Florida, Gainesville, Florida*

Studies in rat isolated hearts suggest that adenosine is more potent for slowing antegrade atrioventricular (AV) than retrograde ventriculo-atrial (VA) conduction. The potency (EC_{50}) and maximal effect (E_{max}) of adenosine to slow AV and VA conductions were determined in 16 patients (mean age 48 years). These patients were selected from a group that had a common form of AV nodal reentrant tachycardia who had prior to the study been subjected to selective radiofrequency ablation of the slow pathway conduction, but with intact antegrade and retrograde fast pathway conduction. During high right atrial and ventricular pacing at comparable cycle lengths (400–500 msec), adenosine was injected as an intravenous bolus at an initial dose of 0.5 mg followed by stepwise increase of 1 mg given every 5 minutes until AV or VA block occurred. The dose-response curves for adenosine-induced pro-